STARGARDT'S DISEASE AND FUNDUS FLAVIMACULATUS: EVALUATION OF MORPHOLOGIC PROGRESSION AND INTRAFAMILIAL CO-EXISTENCE*

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INTRODUCTION

STARGARDT[1] IN 1909 DESCRIBED TWO FAMILIES WITH A FAMILIAL PROGRESSIVE MACulopathy assocaited with perifoveal flecks in most cases. Subsequent reports by Stargardt and others[2-12] have elaborated upon the initial descriptions. Franceschetti[13] later described cases with peripheral fundus fleck lesions that he called fundus flavimaculatus. Since then there has been debate as to whether or not these are two different entities.

This thesis demonstrates, on the basis of a psychophysical longitudinal study and by family studies that Stargardt's disease and fundus flavimaculatus co-exist within families as different phenotypic expressions of the same genotype. A study of 39 family pedigrees, containing 56 affected individuals, confirms (1) that family members may demonstrate either maculopathy or diffuse flecks; (2) that the flecks are of the same morphologic appearance in the two conditions; and (3) that there is a tendency toward progressive retinal degeneration in some affected individuals. Extensive psychophysical testing does not appear to be of predictive value as to which family members will develop progressive retinal degenerations.

HISTORY

Stargardt[1] in 1909 described seven patients from two families with a familial, progressive, bilateral, and symmetrical affliction of the foveal region leading to partial or complete loss of central vision. All patients, both male and female, were confined to one generation suggesting an autosomal recessive inheritance. In separating this macular disorder from other forms of macular degeneration, Stargardt documented the progres-

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sion from an early stage with reduced visual acuity in spite of an ophthalmoscopically normal fovea to a characteristic horizontal oval area of atrophy of the retinal pigment epithelium with a beaten-bronze appearance. In most cases, small yellow-white flecks which surrounded the atrophic area were separated from the latter by a zone of ophthalmoscopically unaffected pigment epithelium. The peripheral fields were normal and there were no complaints of night blindness. Almost 50 years later, two of the original seven patients (of the same family) were reported by Rosehr[2] to be essentially unchanged except for an increased area of macular degeneration. Apparently neither had significant loss of peripheral field nor complaints of night blindness.

The essential features of the prototype disease described in Stargardt's original publication are:

1. Initial loss of vision without definite ocular fundus changes and with an associated mild loss of color vision.
2. Subsequent appearance of an atrophic macular degeneration with flecks developing in the paramacular and posterior eye ground areas. The area of degeneration increases with time and the flecks may disappear.
3. Essentially normal peripheral visual fields and night vision.
4. Autosomal recessive inheritance with the onset of clinical symptoms in the first or second decade.

Continued observations by Stargardt[6] on another pedigree indicated that some cases progressed to involve the peripheral retina in the fashion of a pigmentary retinopathy and which he termed "retinopathia pigmentosa inversa." There were additional findings of severe color blindness, photophobia, and nystagmus. It is unclear whether these cases were the same entity or a form of cone or cone/rod dystrophy. Stargardt[3-5] continued to observe and modify the characteristics of this entity, which became known variously as Stargardt's disease, Stargardt's juvenile macular degeneration, juvenile macular degeneration, or simply Stargardt's maculopathy. More recently the terminology describing this entity, or variants thereof, has expanded to include centroperipheral tapetoretinal pigmentary dystrophy (TRD),[7] macular form of TRD,[8] mixed TRD,[9] and diffuse or central TRD.[10,11] Deutmann[12] added a further descriptive category—"Stargardt's disease with peripheral involvement." He attempted to unify the various descriptive categories by describing three major forms in which Stargardt's dystrophy may become manifest: (1) purely central TRD; (2) central and peripheral TRD; and (3) centroperipheral TRD with or without peripheral field defects.

During the first half of this century the emphasis was on the macular lesion in cases of Stargardt's disease, even though the two colored paint-

ings[1] in 1909 show white flecks to be present. Little attention was directed to the fleck component of the disorder for the next half-century until Franceschetti and later Franceschetti and co-authors[13-16] directed attention to the flecks in a series of publications beginning in 1963. He used the term "fundus flavimaculatus" to describe the appearance of irregularly shaped yellow-white flecks within the retinal pigment epithelium. Although the condition initially was thought to affect only the posterior pole with or without associated macular dysfunction, Franceschetti and co-authors[17] later observed that there were cases intermediate between pure fundus flavimaculatus with no visual disturbance and tapetoretinal degeneration. Emphasis on the flecked component of the disorder continued to increase because of the development of improved diagnostic examination techniques, such as fluorescein angiography.[18,19] Over the following decade, a number of publications concerned with the appearance of the flecks appeared and there was reference to the similarities of the flecks of Stargardt's disease and fundus flavimaculatus.[20-24] Subsequently, progressive changes in fleck characteristics in fundus flavimaculatus were mentioned by many authors, who described the advancement from a picture of localized flecks to an end-stage showing diffuse choriocapillaris atrophy with totally resorbed flecks.[25]

The relationship between Stargardt's disease, ie, Stargardt's hereditary macular dystrophy and fundus flavimaculatus remains controversial as to intrafamilial co-existence and the degree and probability of progressive deterioration of each. The concept that Stargardt's disease and fundus flavimaculatus are the same condition was suggested by the previously mentioned authors and more recently by Krill and Deutman,[26] Irvine and Wergeland,[27] Hadden and Gass,[28] and most recently by Noble and Carr.[29] Krill and Archer[30] emphatically stated that the natural course of fundus flavimaculatus indicates "there is no question that the majority of the cases included under this description are, indeed, examples of the same disease initially described by Stargardt." While favoring a unification of the two disease categories, there is disagreement among these authors as to the existence, or at least prevalence, of variation in expressed characteristics within an individual during subsequent years or within affected family members. Hadden and Gass[26] conclude that, while the severity and appearance of lesions varied, the distribution remained constant giving a similar pattern within any one family. Noble and Carr,[29] on the other hand, found that perifoveal or diffuse flecks subsequently developed in some patients originally having only maculopathy while the reverse occurrence was also present. Thus, whether these two disease

entities should be amalgamated into one, as suggested by Deutman who apparently was the first to use the term "Stargardt's flavimaculatus,"[12,26] still remains in question.

Further disagreement exists among previous authors concerning the possibility or likelihood of progression of the degenerative process within an individual. Krill and Archer[30] state that "in both Stargardt's disease and fundus flavimaculatus, the peripheral visual fields and night vision remain essentially normal." Nevertheless, the same authors later state that "some patients with fundus flavimaculatus develop severe cone abnormalities."[31] Although most reports have observed the proliferation of flecks over years of follow-up, Noble and Carr[29] found that none of their patients progressed to the arteriolar attentuation and chorioretinal atrophy described by Fishman[25] as stage 4 generalized pigmentary retinal degeneration.

It is the purpose of the present study to learn through a systematic evaluation of the probands and their families (1) whether Stargardt's disease and fundus flavimaculatus co-exist within the same pedigree, (2) what variation exists within intrafamilial expression of the dystrophic processes, and (3) to determine, by long duration follow-up by a single examiner, the degree and probability of progressive morphologic and functional deterioration of affected individuals.

SUBJECTS AND METHODS

All consecutive cases of Stargardt's maculopathy and fundus flavimaculatus seen by the author during the past 16 years have been evaluated for parameters of age of symptomatic visual decrease, progress of visual disability and ophthalmoscopic morphologic change, family pedigree, and functional parameters (Table III and IV). Records were consecutively maintained of all probands examined and an attempt made to personally examine all consenting members of each pedigree, whether known to have an ocular disorder or not. Each individual was given a complete ophthalmoscopic examination, including indirect ophthalmoscopy and fundus microscopy. Color fundus photographs were taken of all consenting individuals examined. Fluorescein angiography was performed on all consenting afflicted or possibly afflicted individuals. Electroretinography (ERG), electrooculography (EOG), dark adaptation (DA) testing, and visual field testing (central and peripheral) were performed on all affected consenting patients (Table IV).

Intrafamilial and interfamilial similarity or variation and extent of progression of ophthalmoscopic, functional, and electrophysiological parame-

ters over the follow-up period was documented by records and photographs. Only patients meeting the description of Stargardt's disease, as noted earlier in this thesis, and fundus flavimaculatus were included, while all other forms of infantile, juvenile, or adult dystrophies as well as adults with age-related macular degeneration were excluded. Thirty-nine family pedigrees, containing 56 affected individuals, comprise the present study.

The majority of the family pedigrees, particularly the members of the proband generations, were examined. Electrophysiologic evaluation was performed on 41 of 56 patients. ERG, EOG, both tested by diffuse retinal illumination, DA, and central and peripheral visual field testing was performed on the 41 cases (in rare instances, one or more of the tests were omitted). Eleven patients had color vision testing by Farnsworth-Munsell 100 hue profile.

Four patients were lost to follow-up reexamination. Fifty-two patients had two or more examinations. Of these 52 patients who responded for repeat examination by the author, the mean follow-up examination following initial examination was 6 years with an average of 6.72 years. The range of follow-up was 4 months to 16 years. Eleven patients have follow-up of 8 to 16 years.

The patients were classified into four stages by the description at the time of initial presentation. The staging system (Table I) combines the classification for Stargardt's disease and for fundus flavimaculatus since their respective corresponding stages closely complement each other. The patients were reclassified at the end of the follow-up period. Krill and Archer[31] divided fundus flavimaculatus patients into two "groups." This term does not allow the progression of a patient from one category to another and thus is not a desirable term. Deutmann[12] and Fishman,[25] describing patients with Stargardt's disease and fundus flavimaculatus, respectively, divided patients into various "stages" since the term "stage" is defined as "a period or distinct phase in the course of a disease or any biologic process"[32]; this appears to be the best term to designate the phase of morphologic change, following either stability or progressive change.

RESULTS

The patient data results are listed in Tables III and IV. The mean age of symptomatic visual impairment of the composite group was age 15 years (average age, 17.5 years)—somewhat older than reported with Stargardt's disease maculopathy. When considering only those presenting with Star-

TABLE I: CLASSIFICATION CHARACTERISTICS OF STARGARDT'S DISEASE AND FUNDUS FLAVIMACULATUS

STARGARDT'S DISEASE	FUNDUS FLAVIMACULATUS
Stage I: Purely central macular degeneration with or without perifoveal flecks	Stage I: Macula may be normal or show mottling of pigment epithelial pigment with paracentral white flecks; normal EOG and ERG
Stage II: Central macular degeneration and pericentral flecks extending outside the posterior fundus	Stage II: Extensive posterior and peripheral white flecks; atrophic macular lesion may or may not be present; EOG and ERG are usually normal
Stage III: Centroperipheral retinal pigmentary degeneration with an intact peripheral visual field but pigment migration, depigmentation and normal retinal vessel size	Stage III: Resorbing flecks with pigment epithelial (PE) atrophy; atrophic macular lesion may or may not be present; subnormal EOG and ERG
Stage IV: Centroperipheral retinal pigmentary degeneration with peripheral visual field defects and "bone trabeculae" pigmentation with attenuated retinal vessels	Stage IV: Macular atrophic lesion present with generalized atrophic choriocapillaris; pigment clumping of PE and intraretinal pigment migration; attenuated retinal vessels and constricted peripheral fields; abnormal EOG and ERG

gardt's maculopathy, the mean age of symptomatic visual impairment was 12 years (average age, 13.7 years). Those patients without macular degenerative changes, when symptomatic, presented at a later age. The range of symptomatic involvement was 3 to 71 years. Seventeen patients had symptomatic change in acuity with development of macular lesion as their first visual symptom during the first decade of life; 20 in the second decade; 7 in the third decade; 4 in the fourth decade; 2 in the fifth decade; with single individuals becoming symptomatic at age 62 and 71 years. Ocular changes were detected in four asymptomatic individuals while screening family members. All the individuals becoming symptomatic after the second decade had paramacular and posterior flecks in various stages of atrophy which preceded the macular lesion.

CLASSIFICATION OF PATIENTS

Classification of patients was necessary to prospectively determine whether there was morphologic progression of the dystrophic changes. At the time the study was initiated, experience of previous authors enabled me to delineate criteria for possible progressive stages.[1,5,6,13,17] As further reports appeared,[12,25] and as my experience grew, the characteristics of the stages were stabilized and previous photographs were then examined and reclassified when indicated. The classification characteristics, as presented in Table I, has remained unchanged since 1976.

At the time of initial examination, the majority (84%) of patients were stage I or II (Table II). During the follow-up period, 15 patients (26%) changed to a stage higher in classification. Two patients changed two stages and three patients changed three stages. The advancing pathology (stage) appeared related mainly to the length of follow-up time. The average time of follow-up of those that advanced in classification was 8.7 years as compared to 2.8 years for those that remained in the same classification. While it appears that increased length of observation follow-up increases the likelihood of ophthalmoscopic and functional changes progressing to a higher classification stage, it should be noted that several cases remained at stage I or II classification for many years. As an example, two sisters with stage I central/paracentral pathology had documented nonprogression for 22 and 24 years, respectively (Fig 1A to D). Those patients presenting with macular degeneration and perifoveal flecks had only a 15% rate of progression to a higher stage (4.3 years average follow-up) while those presenting with diffuse flecks, with or without macular degeneration had a 45% rate of progression (5.7 years average follow-up). Whether more of the patients without diffuse flecks will progress to higher stages with extended follow-up is uncertain.

HEREDITARY AND INTRAFAMILIAL CHARACTERISTICS

Sixteen families were noted to have two or more affected members: 13 families had two or more affected members of a single generation (either male or female) compatible with autosomal recessive inheritance. One family had three affected brothers. Another family (Fig 12) had the proband, his brother and two sisters (four of eight siblings) in one generation affected as well as the father and a paternal aunt. This familial pattern was suggestive of an autosomal dominant inheritance but the possibility of the mother as a carrier could not be eliminated. Therefore, with the aforementioned exception, the reported families conform to the reported auto-

TABLE II: CLASSIFICATION OF PATIENTS

	NO AT PRESENTATION	NO AT END OF OBSERVATION PERIOD	NO THAT CHANGED TO HIGHER STAGE
Stage I	36	24	12
Stage II	11	17	2
Stage III	9	10	1
Stage IV	0	5	0
Total	56	56	

TABLE III*: STARGARDT'S DISEASE AND FUNDUS FLAVIMACULATUS CASE DATA

NAME	DIAGNOSIS	AGE FIRST SEEN	AGE ONSET	INITIAL VISUAL ACUITY		INITIAL DATE SEEN	RECENT VISUAL ACUITY		RECENT DATE	FH	FOLLOW-UP (YRS)	STAGE AT PRESEN-TATION	STAGE AT END
				OD	OS		OD	OS					
1. MS	FF	11	7	20/200	20/200	04-12-76	20/200	20/200	05-10-78	Yes	2.00	II	II
2. MZ	FF	19	8	20/200	20/200	01-21-76	20/200	20/200	03-27-85	Yes	9.00	II	II
3. MB	FF	31	9	20/400	20/400	01-07-77	2/400	2/400	11-24-83	Yes	6.00	II	III
4. CD	FF	11	10	20/30	20/60	08-02-72	20/300	20/300	01-03-85	Yes	12.00	I	II
5. SD	FF	12	10	20/200	20/200	04-09-70	20/300	20/200	01-03-85	Yes	14.00	I	II
6. HB	FF	47	12	3/400	3/400	01-07-77	3/400	3/400	01-24-83	Yes	6.00	III	IV
7. TD	FF	19	16	20/50	20/25	04-11-74	20/60	20/30	06-14-77	No	3.00	I	II
8. MG	FF	36	30	20/20	20/60	04-11-73	20/25	20/70	07-18-77	No	4.00	I	I
9. CB	FF	62	62	20/50	20/30	09-15-76	20/50	20/30	09-15-76	No	1.00	III	III
10. KS	FF	26	26	20/20	20/20	07-22-76	20/20	20/20	09-05-77	Yes	1.00	I	I
11. DD	FF	50	50	20/300	20/300	03-14-78	20/400	20/400	10-04-84	No	6.00	III	III
12. JE	FF	25	25	20/20	20/20	02-22-82	20/20	20/20	10-17-85	Yes	3.00	I	I
13. SD	FF	34	34	20/20	20/20	06-11-81	20/20	20/20	04-18-85	Yes	4.00	I	I
14. BW	Starg	10	10	20/40	20/30	12-12-77	20/200	20/200	05-09-85	Yes	8.00	I	I
15. RT	Starg	23	20	20/70	20/200	01-19-77	NA		NA	Yes	—	I	I
16. DW	Starg	45	3.5	10/400	10/400	06-06-74	10/400	10/400	08-09-77	Yes	3.00	III	III
17. WP	Starg	37	4	20/300	20/200	09:03-75	20/300	20/200	10-01-77	Yes	2.00	I	I
18. TW	Starg	17	4.5	20/200	20/200	06-06-74	20/200	20/200	08-09-77	Yes	3.00	I	I
19. JS	Starg	16	4.5	20/200	20/200	04-08-80	NA		NA	Yes	—	I	I
20. AT	Starg	42	5	8/400	20/40	11-30-70	20/400	20/400	No	4.00	I	I	
21. SS	Starg	9	5	20/400	20/200	08-25-69	8/400	20/400	11-10-85	Yes	16.00	I	IV
22. RE	Starg	15	6	20/400	20/300	07-01-76	20/400	20/300	07-02-77	Yes	1.00	II	II
23. MS	Starg	7	6	20/200	20/200	08-25-69	20/200	20/200	11-21-85	Yes	16.00	I	IV
24. JS	Starg	21	7	20/300	20/400	04-08-80	NA		NA	Yes	—	I	I
25. RH	Starg	7	7	20/50	20/50	12-17-74	20/80	20/80	12-05-77	No	3.00	I	I
26. BU	Starg	8	7.5	20/60	20/60	11-11-71	20/100	20/100	01-05-74	No	2.00	I	I
27. BB	Starg	9	8.5	20/300	20/300	02-05-80	NA		NA	No	—	II	I
28. KW	Starg	20	9	20/100	20/400	06-06-74	20/300	20/400	08-09-77	Yes	3.00	II	II

TABLE III*: (CONT'D)

NAME	DIAGNOSIS	AGE FIRST SEEN	AGE ONSET	INITIAL VISUAL ACUITY		INITIAL DATE SEEN	RECENT VISUAL ACUITY		RECENT DATE	FH	FOLLOW-UP (YRS)	STAGE AT PRESEN-TATION	STAGE AT END
				OD	OS		OD	OS					
29. CC	Starg	12	11	20/400	20/400	02-12-75	20/400	20/400	03-17-77	No	2.00	I	I
30. LK	Starg	16	12	20/70	20/70	09-10-75	20/200	20/200	03-14-85	Yes	10.00	I	I
31. MZ	Starg	30	13	20/200	20/200	03-14-74	20/200	20/200	03-27-85	Yes	11.00	I	III
32. SK	Starg	19	16	20/80	20/80	02-09-76	20/100	20/100	09-20-77	No	1.50	I	I
33. LB	Starg	40	18	20/400	20/300	03-09-77	20/400	20/300	08-14-77	Yes	0.33	II	II
34. DA	Starg	49	18	20/400	20/300	03-10-76	20/400	20/300	03-17-77	No	1.00	II	II
35. IN	Starg	44	18	20/400	20/300	06-08-72	20/400	20/300	07-19-77	Yes	5.00	I	I
36. SA	Starg	40	18	20/400	20/300	06-08-72	20/400	20/300	07-19-77	Yes	5.00	I	I
37. BJ	Starg	41	18	20/70	20/70	07-27-76	20/80	20/80	06-30-77	No	1.00	I	I
38. BS	Starg	20	19	20/400	20/30	03-19-84	20/400	20/100	03-14-85	Yes	1.00	I	I
39. MR	Starg	22	21	20/50	20/40	08-09-73	20/80	20/70	03-11-74	Yes	4.00	I	I
40. JW	Starg	22	22	20/200	20/200	03-22-72	20/200	20/200	03-21-85	Yes	11.00	I	II
41. CP	Starg	32	28	20/200	20/200	12-18-74	20/200	20/200	11-06-77	No	3.00	I	I
42. RP	Starg	44	39	20/200	20/200	07-22-75	20/200	20/200	10-01-77	Yes	2.00	II	II
43. WS	Starg	42	42	6/400	20/100	05-03-72	6/400	20/400	03-28-78	No	5.00	I	I
44. LO	Starg	71	71	20/60	20/25	05-06-75	20/70	20/40	05-21-77	No	2.00	I	I
45. FP	Starg	49	18	20/300	20/200	09-17-75	20/300	20/300	10-01-77	Yes	2.00	III	III
46. DN	Starg/FF	18	15	20/200	20/60	09-22-76	20/200	20/100	10-15-77	No	1.00	II	II
47. SE	Starg/FF	9	8.5	20/200	20/200	03-22-78	6/200	20/200	04-18-85	Yes	7.00	I	IV
48. LE	Starg/FF	25	11	20/300	20/300	03-22-78	20/300	20/300	04-18-85	Yes	7.00	III	III
49. CS	Starg/FF	14	14	20/400	20/300	07-31-78	20/400	20/400	05-13-85	No	7.00	II	II
50. PC	Starg/FF	32	16	5/400	20/200	01-29-80	20/400	20/200	11-11-85	No	5.00	III	III
51. LK	Starg/FF	55	20	20/400	20/300	03-25-77	20/400	20/300	08-20-77	Yes	0.33	III	III
52. SB	Starg/FF	23	20	20/100	20/100	02-08-77	20/200	20/200	11-23-82	Yes	5.00	I	II
53. BG (F)	Starg/FF	24	22	20/200	20/50	02-19-79	20/200	20/100	03-18-85	No	6.00	I	II
54. DL	Starg/FF	31	31	20/30	20/25	04-11-79	20/400	20/50	05-11-81	No	2.00	I	II
55. WE	Starg/FF	55	35	20/25	20/400	05-17-78	20/40	HM	04-18-85	Yes	7.00	II	IV
56. EP	Starg/FF	62	40	20/70	20/30	09-20-79	20/400	20/400	10-17-85	Yes	6.00	III	III

*Starg, Stargardt's disease; FF, fundus flavimaculatus; HM, hand motion; NA, not available; OD, right eye; OS, left eye.

TABLE IV*: ELECTROPHYSIOLOGIC AND FUNCTIONAL DATA

NAME	ERG	EOG	DA	FIELDS
1. MS	Decreased b wave C&R; increased implicit time	1.16/1.05	ND	Ring scotoma OU
2. MZ	WNL	1.72/1.55	WNL	Central scotoma OU
3. MB	Decreased b wave C; decreased b wave R	1.48/1.60	Decreased C, R WNL	Ring scotoma OU
4. CD	WNL	1.32/1.58	Decreased C	Central scotoma OU
5. SD	WNL	1.60/1.70	Decreased C	Central scotoma OU
6. HB	Decreased b wave C&R	1.36/1.38	Borderline C&R	Central scotoma OU
7. TD	WNL	ND	Decreased C&R	Central scotoma OU
8. MG	ND	ND	ND	ND
9. CB	Decreased b wave C; decreased b wave R	1.28/1.28	Decreased C, R WNL	Ring scotoma OU
10. KS	WNL	1.98/2.18	WNL	WNL OU
11. DD	ND	ND	ND	ND
12. JE	ND	ND	ND	ND
13. SD	ND	ND	ND	ND
14. BW	ND	ND	ND	ND
15. RT	ND	ND	ND	ND
16. DW	Decreased a&b waves C&R	1.40/1.59	Decreased C, R WNL	Central scotoma OU
17. WP	Decreased a&b waves C; decreased b wave R	2.03/2.60	Decreased C, R WNL	Central scotoma OU
18. TW	ND	ND	ND	ND
19. JS	ND	ND	ND	ND
20. AT	Decreased a&b waves C; R WNL	ND	Decreased C&R	Central scotoma OU
21. SS	Decreased a&b waves C&R	1.25/1.65	Decreased C, borderline R	Central scotoma OU
22. RE	Decreased b wave C&R	1.43/1.32	Decreased C, borderline R	Central scotoma OU
23. MS	Decreased b wave C&R	1.45/1.29	Decreased C, R WNL	Central scotoma OU
24. JS	ND	ND	ND	ND
25. RH	WNL	2.59/2.64	Decreased C, R WNL	Central scotoma OU
26. BU	WNL	1.85/2.04	Borderline	Central scotoma OU
27. BB	ND	ND	ND	ND
28. KW	Decreased b wave C&R; increased implicit time	1.63/1.57	Decreased C, R WNL	ND
29. CC	WNL; increased implicit time C&R	2.10/2.28	Decreased C, R WNL	Central scotoma OU
30. LK	C&R WNL	1.90/2.08	Decreased C, R WNL	Central scotoma OU
31. MZ	WNL	ND	Decreased R	Central scotoma OU

TABLE IV*: (CONT'D)

NAME	ERG	EOG	DA	FIELDS
32. SK	Decreased a&b waves C; R WNL	1.79/1.81	WNL	Central scotoma OU
33. LB	WNL	1.59/1.25	WNL	Central scotoma OU
34. DA	Decreased b wave C; R WNL	1.67/1.60	Decreased C, R WNL	Central scotoma OU
35. IN	Decreased b wave C&R	ND	Decreased C, R WNL	Central scotoma OU
36. SA	WNL	ND	WNL	Central scotoma OU
37. BJ	ND	ND	ND	ND
38. BS	ND	ND	ND	Central scotoma OU
39. MR	Decreased a&b waves C; R WNL	ND	WNL	Central scotoma OU
40. JW	Decreased b wave C; R WNL	2.38/2.33	WNL C&R, C borderline	Central scotoma OU
41. CP	Decreased a wave C; R WNL	3.18/3.01	WNL	Central scotoma OU
42. RP	Decreased a&b waves C; decreased b wave R	2.49/3.01	Decreased C, R WNL	Central scotoma OU
43. WS	Decreased b wave C&R	ND	ND	Central scotoma OU
44. LO	WNL	3.75/2.64	Decreased C&R	Central scotoma OU
45. FP	Decreased a&b waves C>R	1.58/1.63	Decreased C, R WNL	Central scotoma OU
46. DN	WNL	1.39/1.25	Decreased C	Central scotoma OU
47. SE	Decreased a&b waves C>R	1.30/1.55	ND	Central scotoma OU
48. LE	Decreased a&b waves C	1.36/1.47	ND	Central scotoma OU
49. CS	ND	ND	ND	ND
50. PC	Decreased b wave C	ND	Decreased C	Central scotoma OU
51. LK	Decreased b wave C; increased implicit time	ND	WNL	Central scotoma OU
52. SB	WNL	2.75/2.49	Decreased C	Central scotoma OU
53. BG	ND	ND	ND	Central scotoma OU
54. DL	ND	ND	ND	Central scotoma OU
55. WE	Decreased a&b waves C&R	ND	ND	Ring scotoma extends to periphery OU
56. EP	ND	ND	ND	Central scotoma OU

*C, cone response; R, rod response; WNL, within normal limits of laboratory; ND, not done; OU, both eyes.

somal recessive inheritance of Stargardt's maculopathy and fundus flavimaculatus.[1,13,29,33] The final pedigree had two affected cousins.

When the affected members were of similar ages (ie, ages separated by 3 years or less) the symmetry of affection was striking. Nevertheless, in

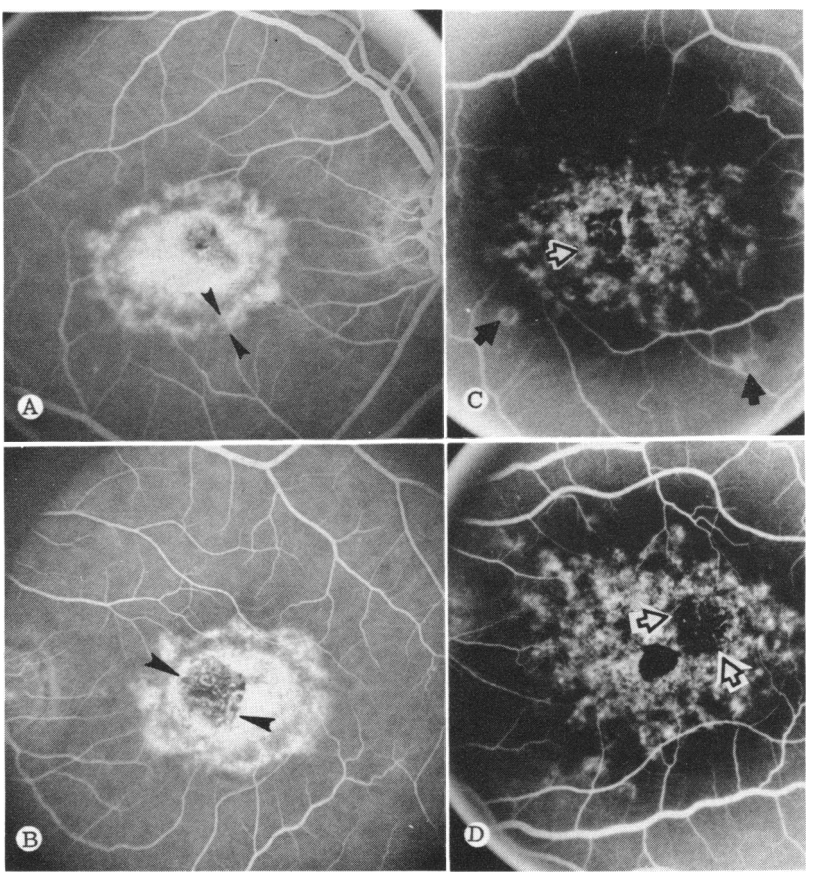

FIGURE 1

Fluorescein angiograms of sisters IN and SA (cases 35 and 36) with stage I, central Stargardt's disease and visual acuity 20/400 both eyes (OU), stable for more than 20 years. A: IN, age 44, right eye (OD) (mid-venous phase) demonstrates central hyperfluorescence due to deterioration of overlying pigment epithelium. Parafoveal ring of white confluent flecks (*arrows*) is separated from central lesion by a narrow zone. B: IN, left eye (OS), demonstrates an area of hypofluorescence (*arrows*) where choriocapillaris is absent showing underlying larger choroidal vessels. C: SA, age 40, OD has less confluent affection of pigment epithelium extending out to major vascular arcades (*arrows*) approaching stage II distribution. D: SA, OS with even broader distribution of hyperfluorescent flecks (*arrows*). Both eyes have areas lacking choriocapillaris (*open arrows*).

spite of similarities of fleck distribution, there were variations of macular dysfunction which persisted for at least 5 years of follow-up (Fig 2A to G) in one pedigree before eventually reaching a level of 20/200 or less in both eyes of both individuals.

When the difference in age of affected members of a generation was greater than 3 years, the asymmetry of ophthalmologic findings as well as functional results were striking. Two cousins (Figs 3 and 4), separated in age by 16 years, initially were very asymmetric showing only flecked lesions and macular dystrophy in the younger female member while showing early pigment epithelial atrophy in the older male member with peripheral field loss. In the subsequent 20-year follow-up, both members developed a similar picture of diffuse pigment epithelial atrophy and constricted fields. Similarly, a brother, age 26, had minimal macular lesions with paramacular flecks (Fig 8), while a sister 2 years older (Fig 7) advanced to diffuse atrophy of pigment epithelium and visual field loss.

One family pedigree had three affected brothers, ages 49, 44, and 37 (Fig 5A to F) at presentation. The oldest showed persistent pigment epithelial atrophy with a central lesion while the youngest showed only the central lesion and perimacular lesions. The middle-aged brother showed an intermediate stage.

Perifoveal flecks resorb with increasing age within the pedigree leaving faint atrophic spots, but the foveal atrophic lesions persists, or increases in size, appearing often as a metallic sheen or atrophic area of pigment epithelium with the underlying choriocapillaris intact. The latter separates the entity from central choroidal dystrophies which can simulate the latter macular lesions once the flecks disappear. Flecks may develop directly in the foveolar area reducing vision without significant initial atrophy of pigment epithelium.

Families with affected members of a similar age distribution often showed symmetry which appears to persist indefinitely (Fig 6A and B). Exceptions were present, as exhibited in the aforementioned brother 2 years younger than his sister (Figs 7 and 8). Both had examinations at the age of 30 years. The brother had only paramacular flecks with normal vision, while at the same age the sister had severe macular dystrophy and loss of central acuity.

Two sisters, ages 5 and 6 at onset of visual symptoms (Fig 6A and B), were initially noted to have typical oval, beaten-metal appearance of the maculas characteristic of Stargardt's disease but 7 years later had developed extensive diffuse flecks, demonstrating the bridge between Stargardt's disease and fundus flavimaculatus within individuals. This bridge between the two disease expressions was also shown by the intrafamilial

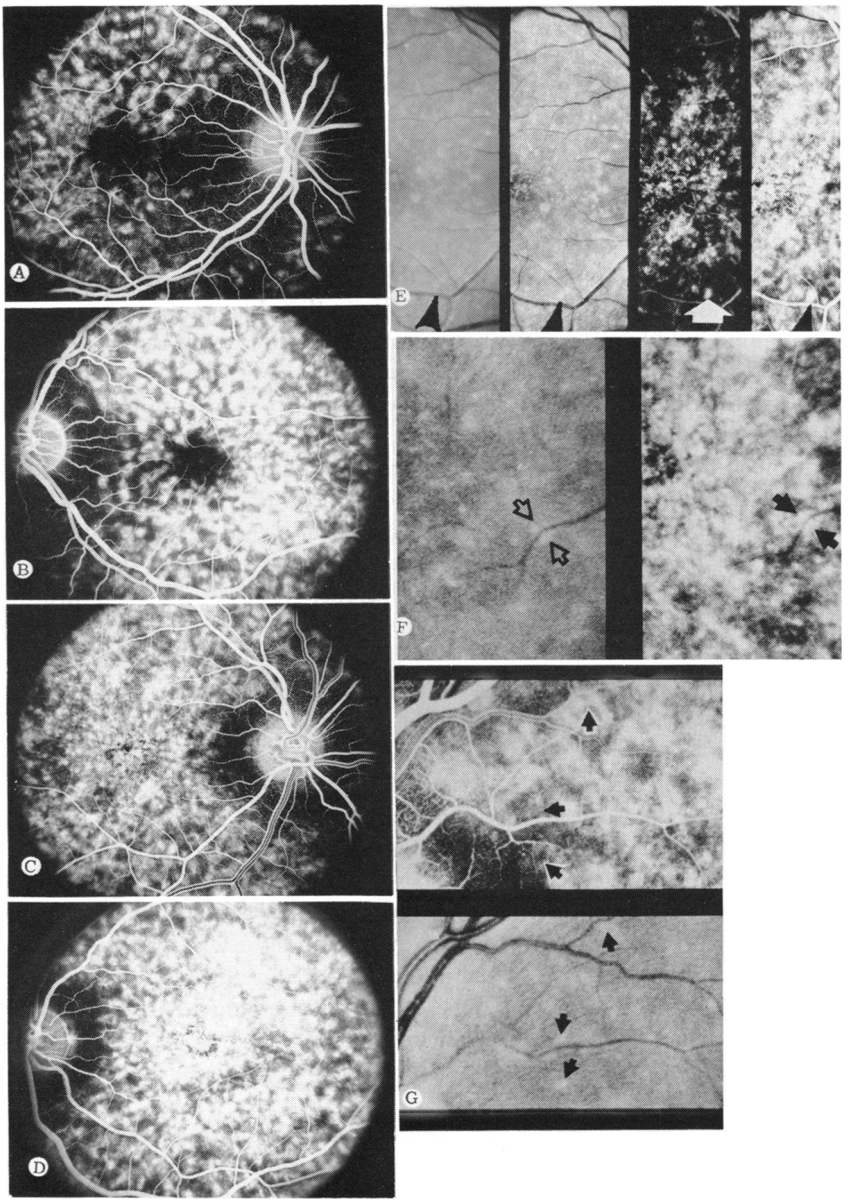
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FIGURE 2

Fluorescein angiograms of sisters CD and SD (cases 4 and 5). A: CD, age 16, OD stage II with stable visual acuity (20/40) but increasing flecks over first 5 years of follow-up. Minimal foveal flecks or dystrophic pigment epithelial (PE) sheen are present. B: CD, OS—visual acuity is also stable (20/50) with close symmetry to fellow eye. C: SD, age 18, stage II with stable acuity (20/200 OU) over the entire 14 years' follow-up. Foveas are involved by dystrophic sheen and PE atrophy has also remained stable. D: SD, OS, has close symmetry to OD and stable acuity. E: This SD series demonstrates that flecks are seen with difficulty in kodachrome (A) but enhanced with a red-free filter (B). Fluorescein angiogram shows fluorescence in early phase (C) and later phase (D). F: Left picture (kodachrome) shows flecks (*open arrows*) which fluoresce in right picture (*arrows*). G: Comparison of fluorescein angiogram (*upper photo*) and red-free photograph (*lower*) shows some flecks (*upper arrow*) fluoresce on either side of fleck while other flecks (*lower two arrows*) do not fluoresce. Continued follow-up (12 and 14 years, respectively) did not demonstrate any morphologic stage change in either individual.

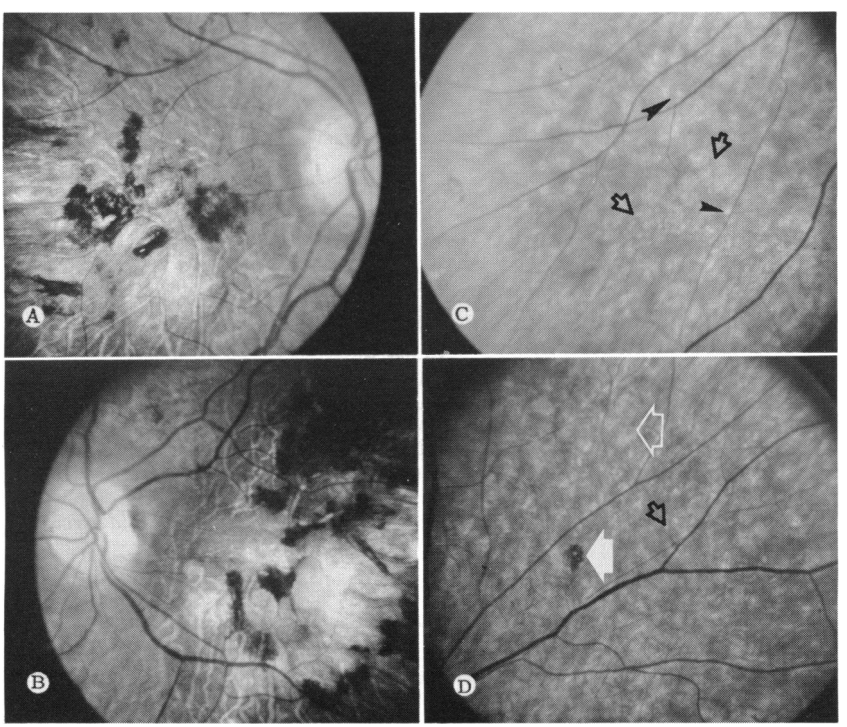


FIGURE 3

MB, (case 3), 31-year-old female has had increased peripheral field loss, decreased flecks and increased atrophy progressing from stage II to stage III over 6 year' follow-up. A: Macula OD has marked atrophy of pigment epithelium and aggregation of pigment (5/400). B: Macula OS has same appearance and acuity. C: Inferotemporal area has remaining flecks (*solid arrows*) and atrophic areas of PE (*open arrows*). D: Supernasal area has similar flecks (*open black arrow*) and intraretinal migration of pigment (*solid white arrow*). Vascular attenuation has not yet occurred so she was in stage III but approaches stage IV.

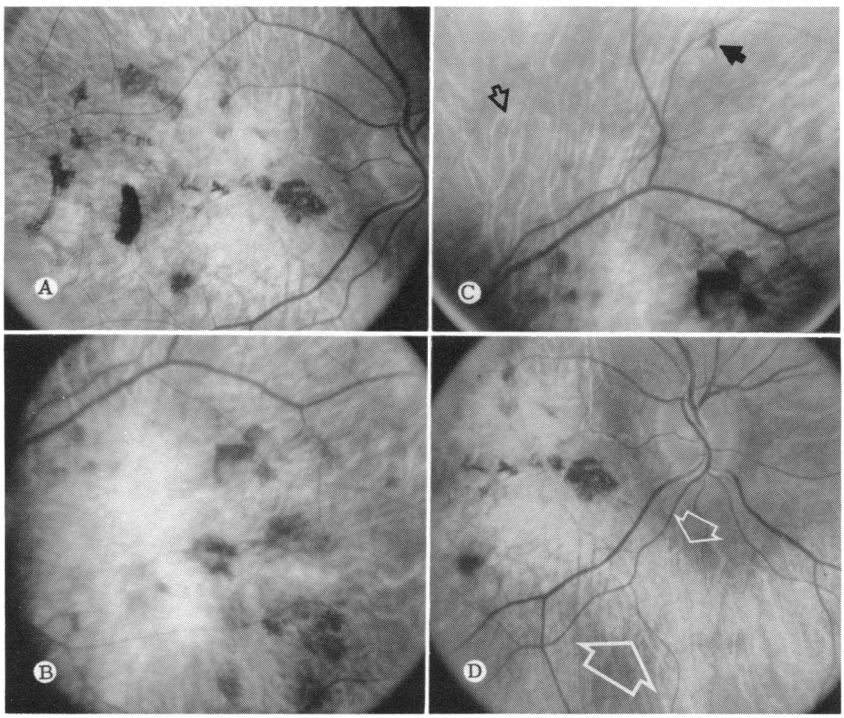
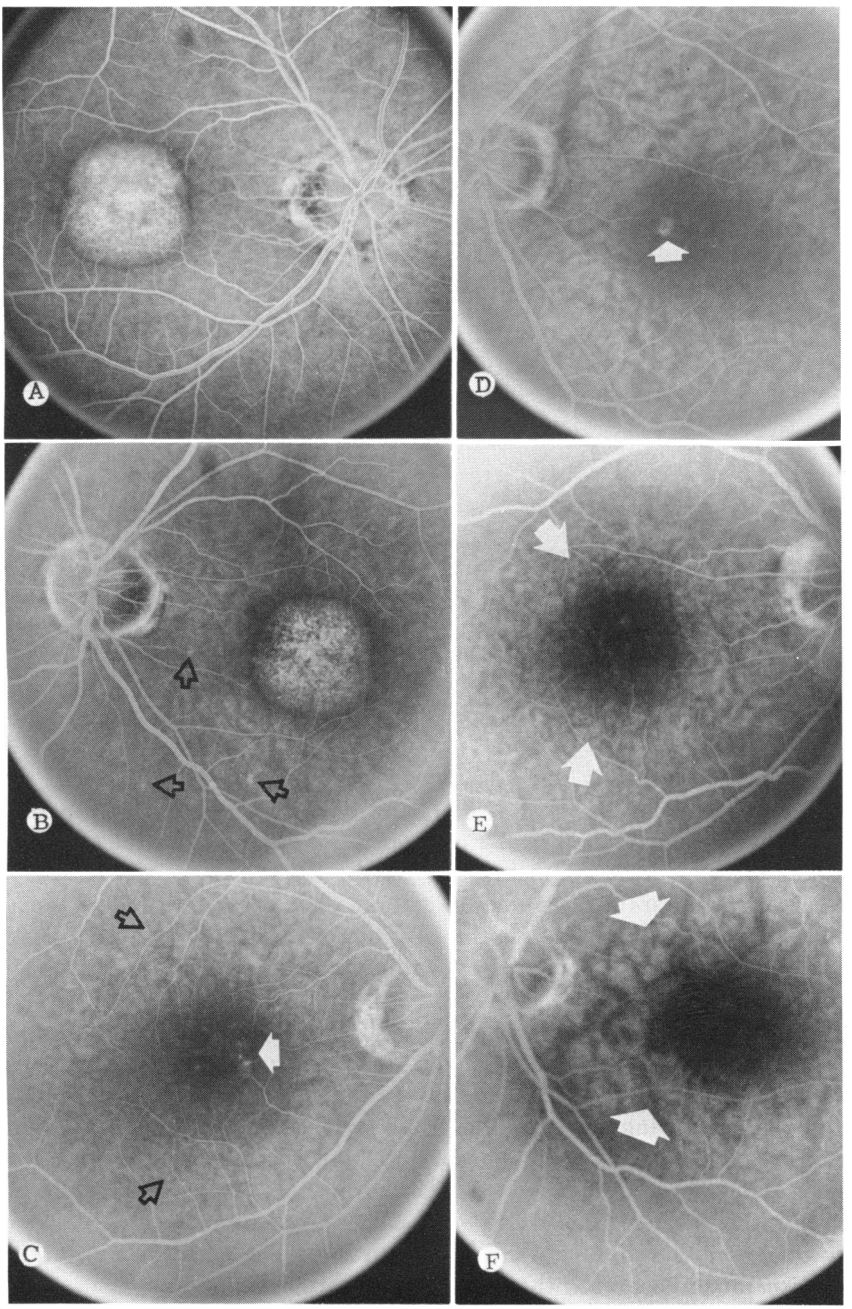


FIGURE 4

HB, (case 6), 53-year-old male cousin of MB, has had increased, marked peripheral field loss, increased PE atrophy, and loss of remaining flecks and vascular attenuation during 6 year' follow-up progressing from stage III to stage IV. A: Macula OD and (B): macula OS have marked PE atrophy with acuity 2/400. C: Superotemporal retina demonstrates PE atrophy peripheral to vascular arcades (*open arrow*) and intraretinal migration of pigment with "bone spicule" configuration. D: Inferonasal retina has a band of PE atrophy where flecks had previously been (*open arrows*) and pigment aggregation (*solid arrows*).

FIGURE 5

Fluorescein angiogram of three brothers with asymmetrical appearance of their fundi but visual acuity of 20/200 OU in all members. A: FP, (case 45), is a 49-year-old with decreased acuity since first decade. He has typical metallic sheen of PE in macula OD without loss of choriocapillaris and abnormal EOG OU. B: Macula OS has same appearance with a few remaining paramacular fluorescing flecks (*arrows*). C: WP, (case 17), is a 27-year-old man who has had decreased vision since his first decade. He has a few perifoveal flecks (*white arrow*) and patchy PE atrophy in parafoveal areas (*open arrows*). EOG is normal. D: A small central area of perifoveal PE atrophy (*arrow*) and subtle patch of PE atrophy is present. E: RP, (case 42), age 44 years, has only had loss of reading acuity for 5 years. A subtle patchy loss of PE is present in parafoveal area OD (*arrows*) and (F): OS, but no definite flecks remain.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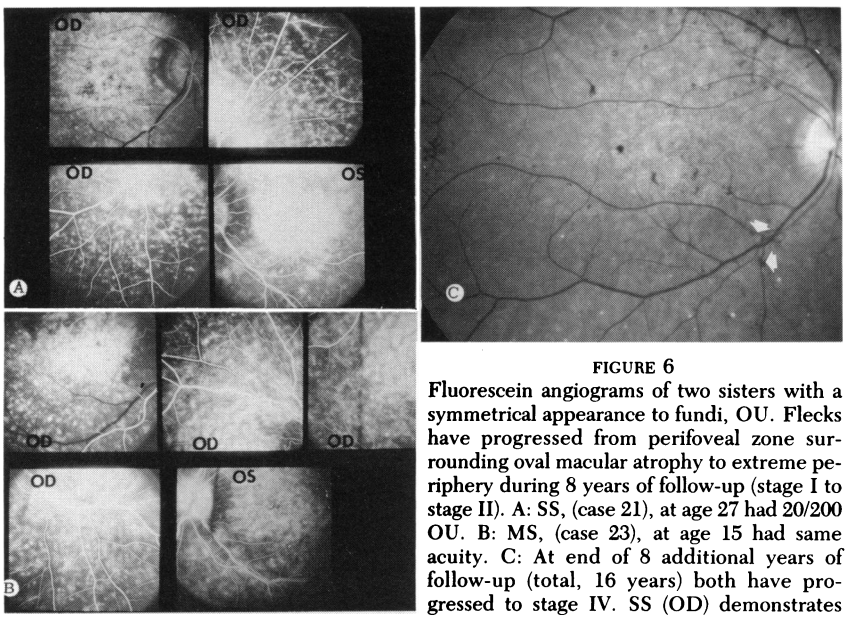

FIGURE 6
Fluorescein angiograms of two sisters with a symmetrical appearance to fundi, OU. Flecks have progressed from perifoveal zone surrounding oval macular atrophy to extreme periphery during 8 years of follow-up (stage I to stage II). A: SS, (case 21), at age 27 had 20/200 OU. B: MS, (case 23), at age 15 had same acuity. C: At end of 8 additional years of follow-up (total, 16 years) both have progressed to stage IV. SS (OD) demonstrates retinal vessels are attenuated with intraretinal migration of pigment and atrophic areas (*arrow*) present where flecks were seen in Fig 6A.

links mentioned before (Figs 1, 6, 7, and 8). Both sisters, over the 16 years I have followed their ocular changes, have progressed three stages, developing pigment epithelial atrophy as the flecks resorbed, arteriolar attentuation, intraretinal pigment migration, extremely large central scotomas, and marked reduction in the ERG amplitudes (the only significant amplitudes recordable in scotopic conditions with high intensity white light).

There appears to be considerable discrepancy between families in regard to morphologic symmetry and degree of progression. Furthermore, there appears to be no certain way to predict intrafamiliar symmetry, some having the affections expressed as macular lesions while others in the family having paramacular or diffuse central flecks (Figs 1, 7, and 8). Other families may have similar ophthalmoscopic appearance but varying affection of visual acuity (Fig 2A to G) during the progressive morphologic deterioration. With long-term follow-up, as in these sisters, the visual functions reach the same level of deterioration.

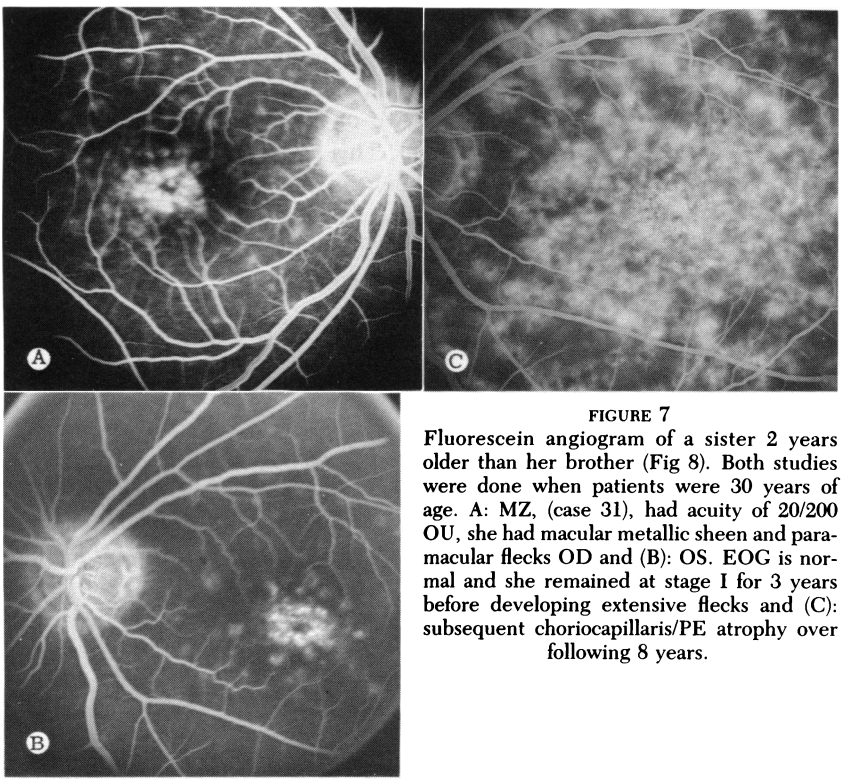

FIGURE 7

Fluorescein angiogram of a sister 2 years older than her brother (Fig 8). Both studies were done when patients were 30 years of age. A: MZ, (case 31), had acuity of 20/200 OU, she had macular metallic sheen and paramacular flecks OD and (B): OS. EOG is normal and she remained at stage I for 3 years before developing extensive flecks and (C): subsequent choriocapillaris/PE atrophy over following 8 years.

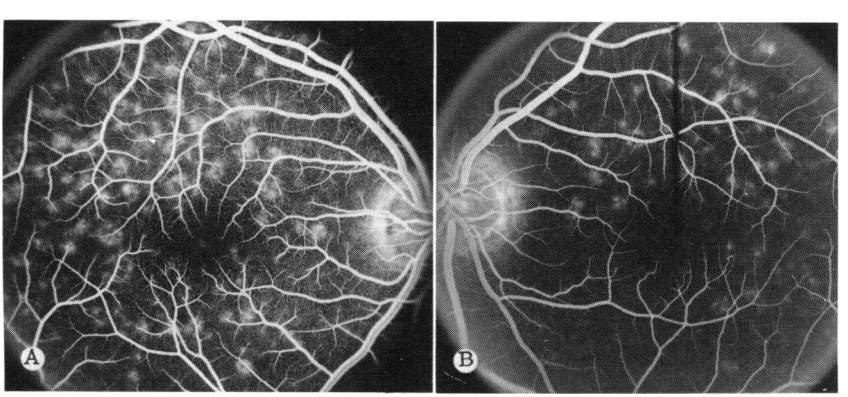

FIGURE 8

KS, (case 10), younger brother of case 31, had asymptomatic changes with 20/20 visual acuity OU when seen for genetic screening. No change occurred in 2 years follow-up with a normal EOG. Paramacular flecks are actually more extentive OD (A) and OS (B) than his affected sister (Fig 7).

SYMMETRY OF FELLOW EYES

The two eyes of each patient demonstrated symmetrical ophthalmoscopic appearance in all but one case. Fifteen patients (26%) had a difference in visual acuity between fellow eyes of two or more lines on the Snellen distance chart upon initial presentation. This asymmetry of visual acuity was present in those presenting with a central oval beaten-metal lesion as well as those with paracentral and diffuse flecks without a typical central lesion. As the patients were followed over 3 or more years, visual acuity between fellow eyes became more symmetrical.

FLUORESCEIN ANGIOGRAPHY

Central (Macular) Lesions

When the primary presenting ophthalmoscopic picture was that of stage I oval, beaten-metal appearance to the macula, hypofluorescence was present in the early stages with increased transmission surrounding the central lesion corresponding to a narrow band of pigment epithelial atrophy. With increasing age, the central lesions lost the metallic sheen and developed areas of atrophy and fluorescein hypertransmission from the underlying choriocapillaris and choroid. The surrounding ring of paramacular white flecks often showed hypofluorescence initially but later hyperfluorescence, indicating uptake (staining) of the fluorescein dye. The paramacular flecks later disappeared leaving hyperfluorescent spots of pigment epithelial atrophy.

The macular lesion, if it developed after prior appearance of posterior flecks, generally had a more atrophic appearance with lesser appearance of metallic sheen—similar to the primary macular lesions at a late stage (Fig 9A to E).

The peripheral flecks are transient in temporal character—usually becoming manifest in the second decade but then appearing and disappearing in various locations over several decades. The flecks may hypofluoresce or exhibit a pattern of hyperfluorescence in a zone surrounding the actual flecks (Fig 2E to G). The variation in fluorescein angiography characteristics probably is related to the age of the fleck, the amount of pigment within the fleck, and degree to which it has affected the pigment epithelium. The degree of pigmentation of the pigment epithelium and choroid is associated with considerable variation in the density of the metallic sheen of the macular lesions. Heavy pigmented patients have an opaque appearing sheen obscuring underlying detail (Fig 10A to D). The sheen also obscures fluorescence of the choroid in the early frames and the sclera, in the late series (Fig 10B to D).

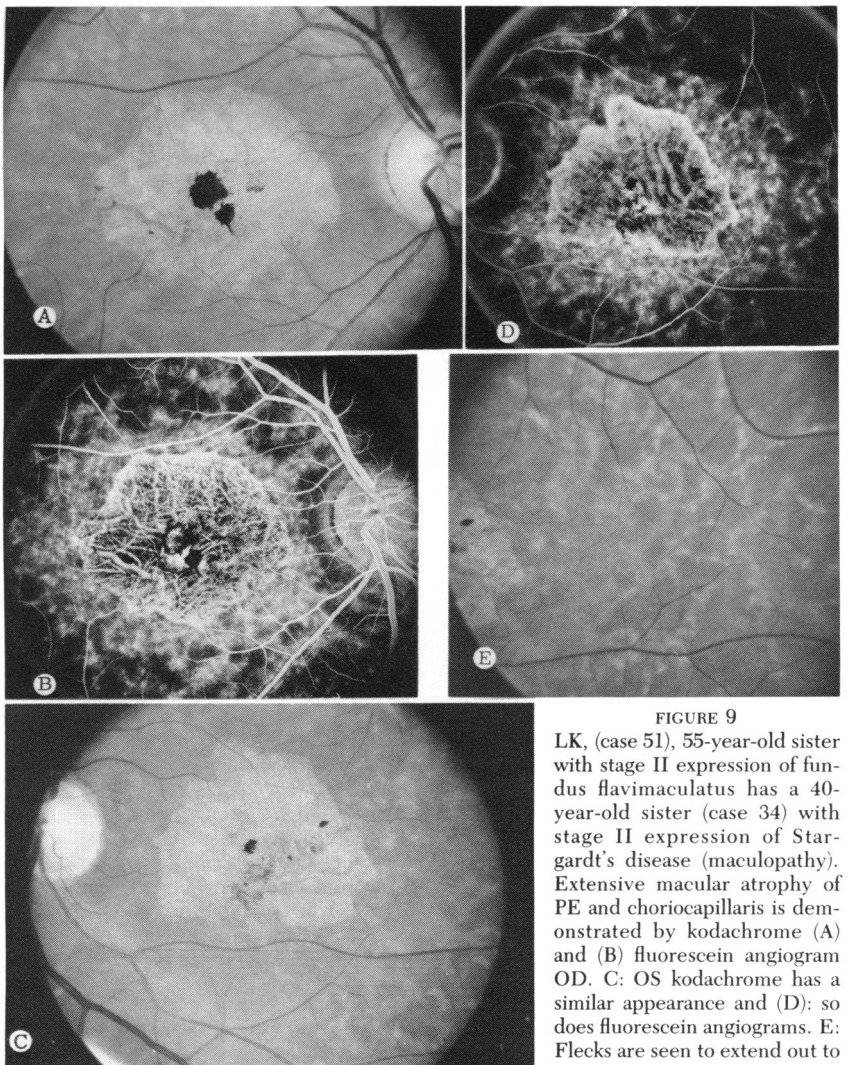

FIGURE 9

LK, (case 51), 55-year-old sister with stage II expression of fundus flavimaculatus has a 40-year-old sister (case 34) with stage II expression of Stargardt's disease (maculopathy). Extensive macular atrophy of PE and choriocapillaris is demonstrated by kodachrome (A) and (B) fluorescein angiogram OD. C: OS kodachrome has a similar appearance and (D): so does fluorescein angiograms. E: Flecks are seen to extend out to anterior equator in OU.

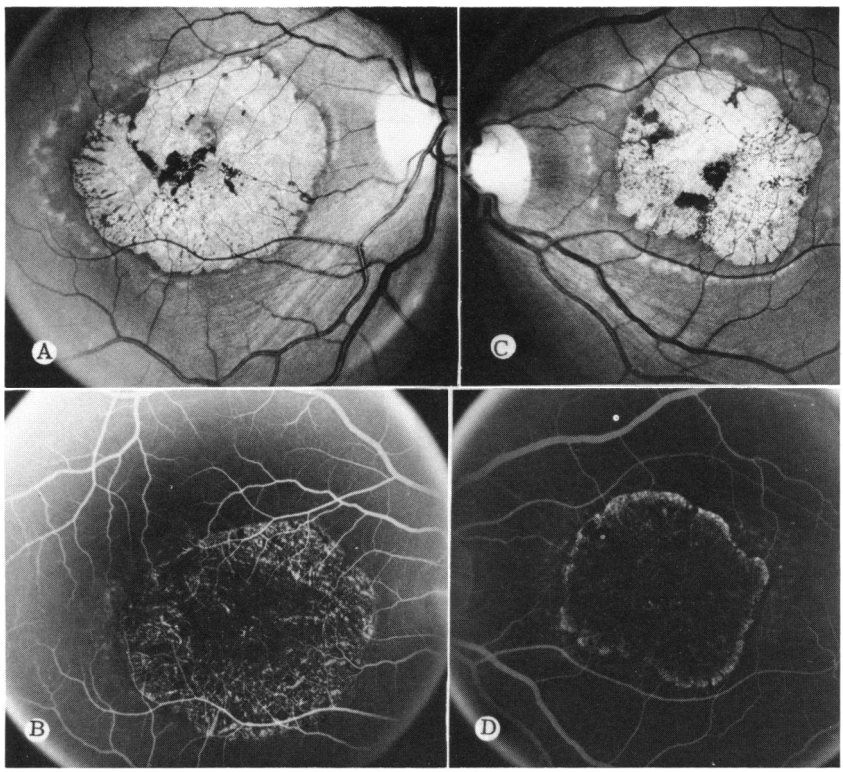

FIGURE 10

WS, (case 43), a 42-year-old female developed decreased vision OU at age 10 to 12 years. Macular metallic appearing lesions have been observed since that time. A ring of white flecks surround densely opaque macular sheen (A & C). No underlying choroidal or scleral detail is visible through opacity. Choriocapillaris fluorescence is barely seen in early fluorescein angiogram (B) of OD due to dense filter-effect of opacity. Late scleral staining is completely obscured except for halo of atrophy at its periphery (C) as seen in late phase of fluorescein angiogram of OS. Flecks stain slightly in late phase.

ELECTROPHYSIOLOGIC EVALUATION

Electroretinogram

Abnormalities in the ERG paralleled the degree of morphologic affection (stage of the disease). Sixteen of 41 individuals tested had a normal ERG. Fourteen percent of those presenting with stage I characteristics had, as the only ERG abnormality, subnormal photopic 'b' wave amplitudes and increased photopic implicit times. Nineteen percent of individuals presenting as stage I had both cone and rod involvement. The remainder had a normal ERG. Since foveal ERGs were not done, this mass cone re-

sponse undoubtedly represents a minimal figure of outer segment dysfunction. Fifty-eight percent of stage II individuals had ERG abnormalities involving decreased 'b' wave amplitudes of both photopic and scotopic responses. All of the seven tested stage III individuals had decreased photopic and scotopic (15-minute DA) 'b' wave. Those (two tested) that progressed to stage IV developed extensive ERG abnormalities. These subjects not only had subnormal 'b' wave amplitudes but also subnormal 'a' wave amplitudes approaching the point of being extinguished in the severe stage IV subjects.

Electrooculogram

The EOG paralleled the ERG; the more extensive the disease process the lower the light peak/dark trough (L/D) ratio. In all cases, as the ratio decreased, it was due to a decrease in amplitude of the peak of the light rise. Fifty percent of the 35 subjects tested had L/D ratio < 1.75 in both eyes. Although the L/D ratio was usually normal in stage I, four stage I subjects (15%) had an abnormally low L/D ratio.

Dark Adaptation Amplitudes

Eighteen of 31 subjects tested had abnormalities of DA. Cone adaptation amplitudes were low normal with an extended time of cone-rod break of 15 to 20 minutes (our laboratory has a normal range of 7 to 10 minutes). Rod amplitudes also took increased time to reach total adaptational amplitudes. In stage III and stage IV subjects, actual adaptational amplitudes of both cones and rods were reduced.

Field Defects

Stage I and II patients had central scotomas of varying density, depending on acuity, but annular (ring) scotomas and generalized peripheral field constriction were noted in stage III and stave IV patients, respectively, as pigment epithelial atrophy vascular attenuation, and pigmentary retinal degeneration progressed.

Color Testing

In the limited number of cases with Farnsworth-Munsell 100 hue testing, an acquired dyschromatopsia of the blue-yellow axis predominated, but all forms of color discrimination dysfunction were present. In the majority of cases, abnormal general color discrimination dysfunction of mild degree was present.

DISCUSSION

Debate has long been present between present authors who consider all macular dystrophies as variations of the same heredodegeneration affect-

ing the posterior pole (stating there are always transition forms linking the various phenotypic manifestations)[34,35] and authors who have classified heredodegenerative central lesions by age of appearance, morphologic appearance, and hereditary characteristics.[36,37] It is accepted, however, that within the specific entity of Stargardt's disease exist interfamilial differences and intrafamilial variation.[17] Similarly, the central lesion may change during the course of the disease. It is in fact documented that lesions at differing stages of development may be found in the same patient.[38,39] The lesion has been described as unilateral as well as paramacular.[17]

The present series documents the above mentioned intrafamilial variations and similarities. By long-term follow-up of affected individuals by the same examiner, this series shows that a single patient may demonstrate differing morphologic manifestations during follow-up intervals bridging the morphologic expressions of Stargardt's disease and fundus flavimaculatus. The variation between eyes, within an individual, is early within the course of the dystrophic development. In cases with atrophic macular lesions, the visual acuity has usually decreased by the end of the second decade to a level where both eyes have equal dysfunction (usually no macular function) as demonstrated by patients 14 and 44. These two siblings, first seen at ages 10 and 22 years, respectively, showed intrafamilial variations in visual acuity and morphology, on presentation. The younger sibling had a slight difference in acuity between her two eyes on presentation, but after 8 years of follow-up (at age 18 years) her visual acuity had decreased to equal levels in both eyes and was then the same as her 10-year-old brother. The morphologic staging at final examination had not changed in the younger sibling, despite the decrease in acuity. The older brother's staging (stage I at presentation, the same as the sisters final stage) advanced to stage II at age 33 years. Therefore, it is probable the younger sibling will advance as her chronologic age progresses. The transition stages between individuals of different generations of a pedigree were found to progress from minimal ophthalmoscopic macular lesions to extensive central-peripheral pigmentary degeneration (Fig 11A to H).

Fundus flavimaculatus has also been noted to have intermediate expression between the original description of the entity, ie, cases with no visual impairment, and extreme cases advancing to pigmentary retinal degeneration.[13,25] In most cases, the distribution of flecks is quite symmetrical within the two eyes of an individual. Vision may vary considerably between eyes of an individual, depending on whether the flecks and/or atrophy affect the foveolar area.[40] While homogeneity of fundus

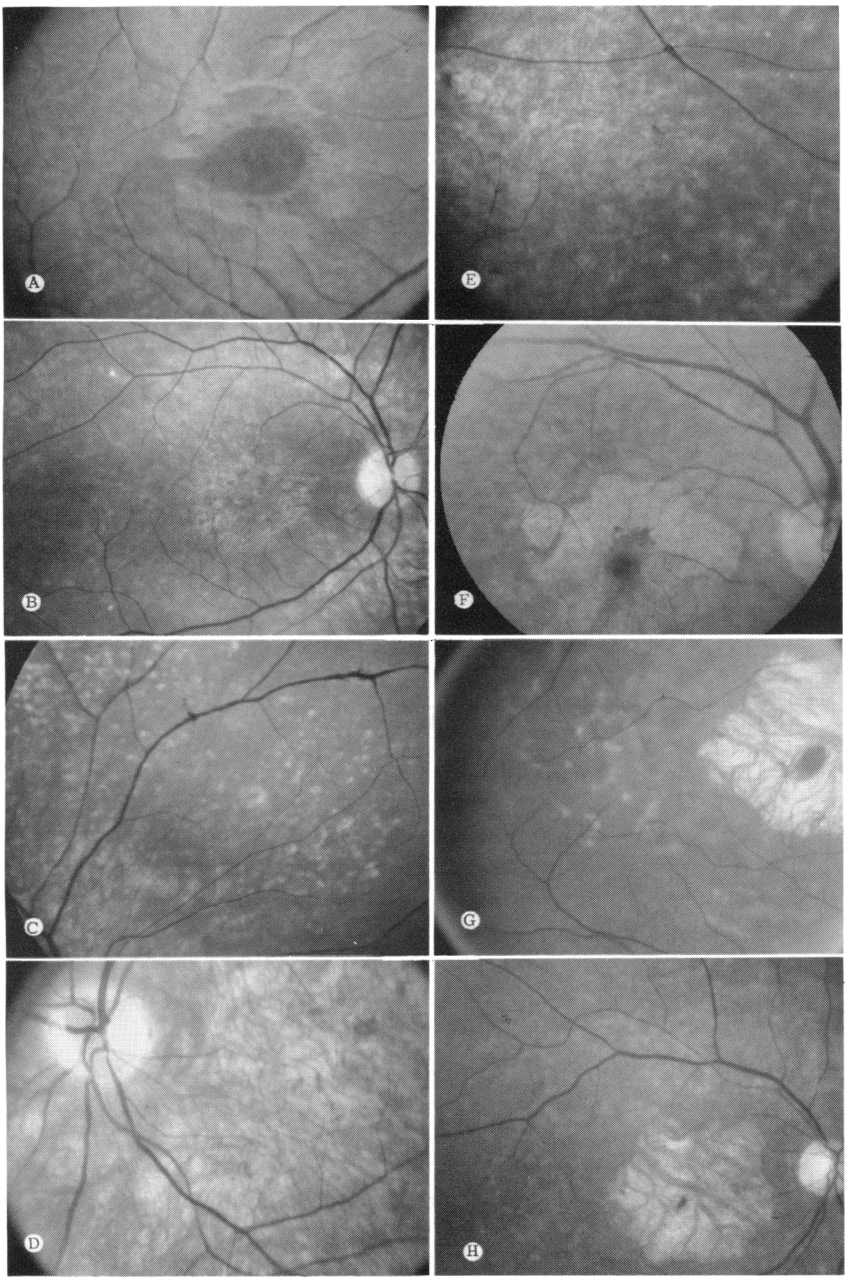
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FIGURE 11

A pedigree of six affected members in two generations. SE, (case 47), age 9 years, when first seen had a "beaten metal" appearance of maculas without atrophy of PE. There were a few temporal perimacular flecks (A) in 1978 (visual acuity, 20/200 OU). These are characteristics described by Stargardt in 1909[1]; 7 years later (B) he has deteriorated to stage IV with retinal vascular attenuation, atrophy of PE in areas of flecks, restricted visual fields; and (C) intraretinal pigment migration present in periphery. D: LE, (case 48), is a 25-year-old sister of SE with an atrophic macular lesion OU and residual flecks (E). She had stage III when first seen and has remained in same stage for 7 years. F: WE, (case 55), is father of SE and LE. He has an atrophic macular change OU (ring scotoma OD, central scotoma OS) which progressed to pigmentary retinal degeneration in 7 years of follow-up. G: EP, (case 56), is a sister of WE and demonstrated perimacular PE atrophy OU when seen at age 62 with temporal flecks as seen in kodachrome of OD. H: Seven years later residual foveal PE had atrophied as seen in kodachrome of OD with visual acuity 20/400 OU.

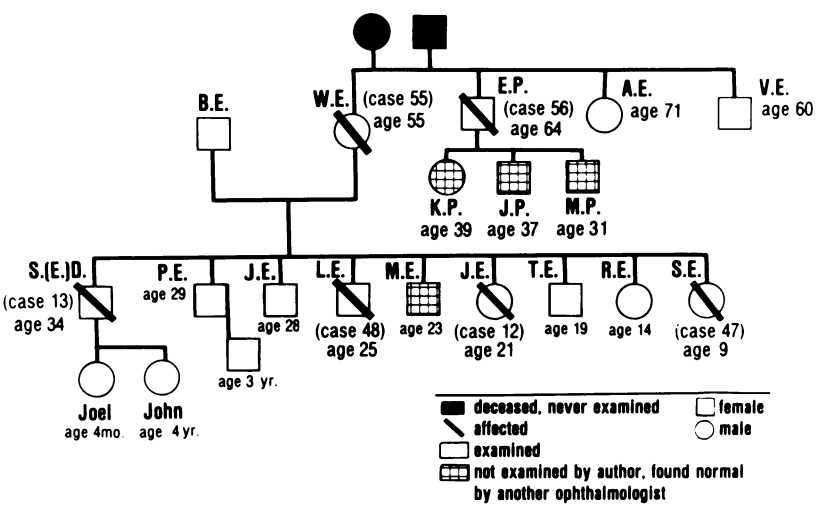

FIGURE 12

This is family tree of pedigree whose photographs are in Fig 11. Affected individuals are known to be present in two generations.

fleck distribution is the rule between eyes of an affected individual, it may not be homogeneous between affected members of a single pedigree. Cases 4 and 5 are examples of intrafamilial difference in expression but such asymmetry disappears as the patients advance in years. The ophthalmoscopic appearance thus depends on the maturation of the disease process.

Since the first histopathologic report of a case of fundus flavimaculatus in 1967 by Klein and Krill,[41] elaborated upon by Newell and co-authors,[42]

it has been known that pathologic changes are principally in the pigment epithelial cell characterized by deposits of acid mucopolysaccharide, possibly hyaluronic acid. A subsequent report found the accumulated material to be a lipofuscin-like substance.[43] This lipopigment was diffuse ("massive") in amount, more aggregated in scattered mounded areas. The greatest concentration was in the posterior fundus. These findings have striking clinical correlations. The aggregated material corresponds to the pisciform flecks. Diffuse deposition would provide generalized obstruction to the transmission of choriocapillaris fluorescence on fluorescein angiography accounting for the dark fundus appearance.[44] As the deposited material destroys the cell, the cell atrophies leaving localized and eventually diffuse areas of retinal pigment epithelial atrophy. The time varies within a given individual and within families.

It is therefore apparent that both entities, Stargardt's disease maculopathy and fundus flavimaculatus, have characteristics very similar, if not identical, in nature with an eventual end-point in many instances which is identical. The various transition phases tend to link the two entities (Figs 1, 3, 4, 7, 8, and 10). A common format linking the transition forms of Stargardt's disease maculopathy and fundus flavimaculatus is presented in Fig 13.

The intrafamilial variation observed in this series reflects the polymorphic expression of the disorder. Two pedigrees (cases 10 and 31 and 35 and 36) had one individual with typical Stargardt's maculopathy and another with diffuse fundus flavimaculatus fleck distribution. In one of these pedigrees (cases 10 and 31) a member (case 10) with widespread flecks had no macular disturbance and normal visual acuity. Another pedigree (cases 21 and 23) presented as typical Stargardt's disease macu-

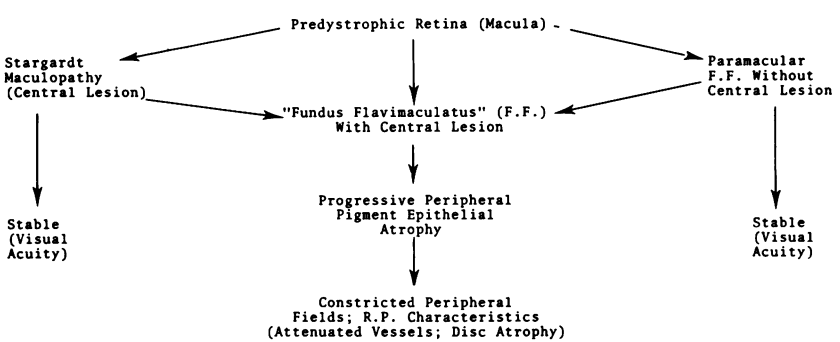

FIGURE 13
Schematic of polymorphic expressions of Stargardt's disease and fundus flavimaculatus variants.

lopathy but, over a period of 8 years follow-up, developed widespread flecks (variable time intervals of fleck expression in the two individuals). Over the subsequent 8 years (total, 16 years follow-up), both progressed to stage IV pigmentary retinal degeneration (vascular attenuation, intraretinal pigment migration and extensive atrophy of choriocapillaris/pigment epithelium).

Another pedigree (cases 33 and 51) had stage II expression of Stargardt's disease in the 40-year-old sister and stage II expression of fundus flavimaculatus in the 55-year-old sister. One pedigree demonstrated both progression and variation in expressivity (Fig 12). A female, seen at age 25 years (case 48, Fig 11D and E), had an atrophic maculopathy with widespread flecks. Over a course of 7 years she remained at the same stage of morphology. The youngest member (case 47, Fig 11A to C) at presentation, age 9, had the appearance of Stargardt's disease with few flecks localized temporal to the macular lesion, the latter characterized by a metallic atrophic sheen. Within 7 years of follow-up he deteriorated to stage IV (three-step change) with marked pigmentary retinal degeneration of vascular attenuation, intraretinal pigment migration, and extensive atrophy of choriocapillaris/pigment epithelium. An older relative (case 56, Fig 11G and H) has been followed by another retinal consultant for 30 years with fundus flavimaculatus fleck appearance and good retention of vision. When first seen by myself, the described flecks had left localized atrophy of pigment epithelium and choriocapillaris after disappearance of most of the flecks. The atrophic areas had not become confluent. Visual acuity gradually decreased over 7 years follow-up due to development of cataract and atrophic macular deterioration. A brother (case 55, Fig 11E and F) of the latter individual, and father of cases 12, 13, 47, and 48 had macular atrophic lesions, asymmetrically greater in the left eye. Confluent chorioretinal and pigment epithelial atrophic lesions extended in a broad ring about the posterior fundus. Ring scotomata corresponded to the atrophic zone and, over the 7-year follow-up, asymmetrically extended into the macula and to the periphery (left eye deteriorating more than the right eye). Two family members (cases 12 and 13) have only scattered flecks without lesions in the macula. Visual acuity is normal in both. Neither of the latter two patients have shown morphologic progression (despite being in the third and fourth decades of life, respectively). This is the sole pedigree in this series which hints at dominant transmission. Other reports[29,45,46] have had isolated single pedigrees with the same dominant pattern causing one author[46] to speculate that Stargardt's disease can result from two different genes. Certainly an unrecognized carrier spouse is another explanation.

The intrafamilial co-existence of both the expressions of Stargardt's disease and fundus flavimaculatus, as well as the progression within an individual of typical Stargardt's disease without diffuse flecks to later Stargardt's disease and diffuse fundus flavimaculatus (cases 21 and 23) indicates there is no clear distinction between the two entities. Nevertheless, within a given pedigree, the present data indicates there is a great latitude of morphologic expression: (1) either solely Stargardt's disease (maculopathy) or fundus flavimaculatus, but not both, or (2) expression of both entities within the same pedigree. The report of Bessiere and co-authors[47] describe an interesting variation of expression. Case 13 of their series has macular degeneration combined with diffuse distribution of fundus flavimaculatus flecks confined to a single sector of the fundus. The present data adds support to the suggestion that the two entities can co-exist within the same family, possibly as a single atrophic process.[12,26-29,45,46] The classification suggested by Deutman[48] which includes Stargardt's maculopathy and fundus flavimaculatus would limit the latter to include only those patients having fundus flecks without an atrophic appearing macular lesion. This would eliminate those families that include both individuals exhibiting only flecks and other members with atrophic lesions (Figs 7 and 8). Any combined classification scheme must recognize and include all the variations of expression documented in this series by chronologic follow-up.

Disagreement exists in the literature as to whether functional deterioration (visual field constriction, decreased night vision, and decreased ERG amplitudes) occur in either Stargardt's disease or fundus flavimaculatus or whether such cases represent other dystrophic entities.[30,31] The pedigrees in this thesis have all the fleck characteristics of Stargardt's disease and fundus flavimaculatus and thus do not represent other dystrophic entities. Some individuals in the pedigree remain at a plateau of morphologic and functional nonprogression and would not be disputed as individuals affected with Stargardt's disease or fundus flavimaculatus. Furthermore, two of the individuals (cases 3 and 6) that later progressed to stage IV pigmentary retinal degeneration were initially diagnosed in the late 1960s as having fundus flavimaculatus by the same authors[31] that questioned whether such functional and morphologic deterioration occurs. Long follow-up is necessary to determine whether deterioration will progress.

Stargardt's disease and fundus flavimaculatus have many features in common, the most dichotomous being the possibility of remaining stable at a given stage for an indefinite period of time or else progressing in a centrifugal fashion with atrophy of pigment epithelium, photoreceptor of

the sensory retina and choriocapillaris. Stargardt[6] observed the possibilities of both indefinite morphologic plateau as well as continued progression to advanced pigmentary retinal degeneration. Francois and DeRouck[49] substantiated the diffuse affection of some cases of Stargardt's maculopathy by showing that, despite ophthalmoscopic and visual function manifestations of a localized macular process, the pathological alterations of the ERG were those associated with diffuse retinal dystrophy. Franceschetti and Francois[15] left open the possibility of progressive abiotrophy in the early reports on fundus flavimaculatus in which they stated that, while central vision may decrease, "the peripheral visual field remains in any case complete." However, Franceschetti[16] hedged this statement by stating that only the further experience by other observers would determine whether the entity was stable or progressive.

Progressive central and paracentral visual field defects have been reported. Passmore and Robertson[50] noted ring scotomas to develop in six patients with fundus flavimaculatus, despite normal visual acuity. They felt this was an ominous sign because 50% of their cases progressed to loss of central vision within 4 years. Isashiki and Ohba[51] described two siblings with fundus flavimaculatus expression in which the brother, with a ring scotoma, showed gradual loss of vision from increasing central involvement while his sister, with diffuse fleck distribution but no macular involvement and no ring scotoma, had no functional deterioration. The follow-up interval was too short to allow definite conclusions, however. My results presented in this current series agrees that progressive deterioration of morphology and function may occur but disagrees with the implication[25] that progression is the rule or inevitable. It is acknowledged that any staging classification is arbitrary, but based on the present classification only 26% of cases advanced in staging during the follow-up period. More may advance as time progresses but several have remained at a plateau for many years.

A recent evaluation of electrophysiologic function in fundus flavimaculatus led Moloney et al[52] to conclude "the dystrophic process of fundus flavimaculatus is progressive," finding the earlier the onset of symptomatology the more severe the deterioration of morphology and function. These authors did not find Stargardt's maculopathy to have significant correlation between duration of affliction and function. My results are in accordance with the latter view. While both Stargardt's disease and fundus flavimaculatus occurred in the same pedigree (Figs 1, 7, and 8), the diffuse fleck expression of fundus flavimaculatus had the greater tendency to progress. Five of 32 patients (15%) with the macular expression of Stargardt's disease progressed an average of two stages over an average

follow-up period of 4.4 years while 10 fo 24 (42%) cases with fundus flavimaculatus, with or without macular lesions of Stargardt's disease, progressed an average of 1.3 stages over an average follow-up period of 5.2 years. Thus a greater percentage of cases with the appearance of fundus flavimaculatus deteriorated morphologically, ie, developed progressive pigment epithelial and choriocapillaris atrophy and pigmentary retinal degeneration in the final stage, than did those with Stargardt's disease variant. The degre of deterioration (as staged) was the same over similar average follow-up. Two of 33 cases with Stargardt's disease deteriorated to stage IV while 3 of 24 cases of fundus flavimaculatus deteriorated to stage IV.

An examiner may be confused when presented with an individual in the advanced stages of the dystrophic process, if no affected family members or family history are available. This probably is the explanation for various reports of Stargardt's disease and retinitis pigmentosa appearing in the same individual[53-55] (ie, these probably represent advanced stages of the dystrophic process). Therefore, in addition to the great variations of intrafamilial and interfamilial morphologic expression, there is an equally great variation in the degree of progression of morphologic and functional deterioration. The progression may plateau for varying periods of time, either temporary or indefinite. The present data indicates that cases which develop fundus flavimaculatus expression have the greatest likelihood of progression with long-term follow-up. It is to be reemphasized, however, that there is *no* evidence in the present data that, when progression to advanced stages is documented, eventual progression to end-stage pigmentary retinal degeneration is inevitable. The present data indicates progression may be aborted at any stage.

Characteristic of the progressive nature is the electrophysiologic profiles during each stage. Individuals with purely a central lesion and a small zone of paramacular flecks have normal ERG, EOG, and DA results, in agreement with previous reports.[25,52,56] If the affection progresses toward the periphery and, as pigment epithelial atrophy ensues, functional tests become increasingly abnormal. While Franceschetti and Francois[56] found a subnormal ERG in only 1 of 30 patients with diffuse flecks, and Carr[57] found a normal scotopic ERG in 5 similar patients, Fishman[25] found the ERG, EOG, and DA to be uniformly normal in only the early stage.

In the present series, the ERG in 7 of 11 tested patients (64%) presenting as stage II (Table I) showed reduced photopic 'b' wave amplitudes while stage III and stage IV progressed to reduced photopic and scotopic 'b' wave and 'a' wave amplitudes. The EOG findings, as in a previous

report,[58] indicated a similar trend. Sixty-nine percent stage I individuals tested had a normal EOG while 20% of stage II tested patients had a normal EOG and none of stage III patients had a normal EOG ratio. Only patients with advanced and extensive disease (ie, more than the posterior fundus) have clearly abnormal EOG L/D ratio.

DA findings were similar to reports of previous authors.[25,26] In stage I and II, cone and rod thresholds were within normal range but the time interval to achieve maximal amplitudes was increased. Final cone amplitudes were reduced in four of the seven tested stage III individuals with both rod and cone amplitudes reduced in the two individuals by the time they progressed to stage IV.

The present study does not implicate an inevitable steady progression from one stage to another, but it does agree with previous reports of possible progression within any pedigree, whether the initial affection is a central lesion[1,6] or flecks of the posterior pole.[25] Individuals in this series with extensive fleck distribution have the greatest likelihood of progression to extensive pigmentary retinal degeneration. Nevertheless, intrafamilial variability in expression dictates caution in extrapolating prognosis from one affected family member to others in the same family. Furthermore, this series supports the previous reports[12,25,28,29,59] which note remarkable similarities between the entities of Stargardt's disease and fundus flavimaculatus with occurrence of both entities within single pedigrees. The clinical evidence adds validity to consideration of the various manifestations of expressivity as part of a general spectrum of a single hereditary disease.

CONCLUSIONS AND SUMMARY

The analysis of families with Stargardt's disease and fundus flavimaculatus lends support to the concept that these two processes are different phenotypic expressions of a common genotypic disease. The points supporting this conclusion are the following:

1. Pedigrees are presented with individuals having typical Stargardt's disease with expression only as maculopathy in one affected member and typical fundus flavimaculatus expression within a second affected member.

2. Patients are presented with typical Stargardt's disease macular lesions that later deveop the typical flecked dystrophy pattern of fundus flavimaculatus.

3. No difference is noted between the characteristic flecks of Stargardt's disease adn the diffuse flecks of fundus flavimaculatus. They are

similar in their morphologic appearance, fluorescein angiographic characteristics and temporal appearance and disappearance.

Definite progression of morphologic and functional deterioration is documented both in patients presenting with Stargardt's disease and those with fundus flavimaculatus. Of the former, 15% advanced an average of two stages in the presented classification while 42% of the later progressed an average of 1.3 stages. Only 26% of the overall series showed stage progression, however, so that there is no evidence for inevitable deterioration presented in this series.

No definite predictive value has been demonstrated for the electrophysiological parameters of ERG, EOG, DA, or color vision testing for prognosis concerning progression of the process, whether it be a localized macular lesion or diffuse flecks. Test values correlate with, but lag behind, progression of the disease rather than herald the onset of general pigmentary retinal degeneration. Individuals with extensive diffuse fleck distribution have the greatest likelihood of progression to severe pigmentary retinal degeneration. Progression to this end stage is documented for both cases presenting as Stargardt's disease and those presenting as fundus flavimaculatus.

All but one family demonstrated autosomal recessive inheritance, as originally described for both Stargardt's disease and fundus flavimaculatus. Other patients might have macular lesions which resemble these entities but have other hereditary patterns. These patients should be viewed cautiously possibly representing similar phenotypic expression of a different genotypic disorder that can only be properly diagnosed by longitudinal study within a family pedigree or long-term chronological evaluation of the patient.

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